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APF	APPLICATION NO. FILING DATE			FIRST NAMED INVENTOR					ATTORNEY DOCKET NO.		
	08/435,	510 05	/05/95	VALLE			F	G(CL266		
Γ				18M2	2/0503	一	PROU	EXAMINER			
		R INTERNA BALL WAY	ATIONAL	INC			ART UNIT	PA	PER NUMBER		
	SOUTH S	AN FRANC	ISCO CA	94080			18	14	#4		
							DATE MAILED:	1	05/03/96		

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks



Application No.

08/435,510

Applicant(s)

Valle et al.

Office Action Summary Examiner

Rebecca Prouty

Group Art Unit 1814

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Responsive to communication(s) filed on	
☐ This action is FINAL .	
☐ Since this application is in condition for allowance except for in accordance with the practice under <i>Ex parte Quayle</i> , 1935	C.D. 11; 453 O.G. 213.
A shortened statutory period for response to this action is set to is longer, from the mailing date of this communication. Failure to application to become abandoned. (35 U.S.C. § 133). Extensio 37 CFR 1.136(a).	respond within the period for response will cause the
Disposition of Claims	
	is/are pending in the application.
Of the above, claim(s)	is/are withdrawn from consideration.
Claim(s)	
Claim(s)	is/are objected to.
☐ Claims	are subject to restriction or election requirement.
Application Papers ☑ See the attached Notice of Draftsperson's Patent Drawing ☐ The drawing(s) filed on is/are object	ted to by the Examiner.
☐ The proposed drawing correction, filed on	is \square approved \square disapproved.
\square The specification is objected to by the Examiner.	
\square The oath or declaration is objected to by the Examiner.	
Priority under 35 U.S.C. § 119 Acknowledgement is made of a claim for foreign priority to	under 35 U.S.C. § 119(a)-(d).
☐ All ☐ Some* ☐ None of the CERTIFIED copies of	the priority documents have been
received.	
received in Application No. (Series Code/Serial Num	
$\hfill\Box$ received in this national stage application from the	International Bureau (PCT Rule 17.2(a)).
*Certified copies not received:	
Acknowledgement is made of a claim for domestic priorit	y under 35 U.S.C. 3 119(e).
Attachment(s)	
X Notice of References Cited, PTO-892	O(c)
Information Disclosure Statement(s), PTO-1449, Paper NInterview Summary, PTO-413	O(3).
 ☑ Notice of Draftsperson's Patent Drawing Review, PTO-94 	18
☐ Notice of Informal Patent Application, PTO-152	
SEE OFFICE ACTION ON T	THE FOLLOWING PAGES

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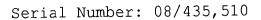
The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and use the entire scope of the claimed invention.

Applicants claim a method for increasing the carbon flow from any carbon source into any metabolic pathway of any host cell. However, the specification shows only increasing the carbon flow from glucose as a carbon source into the common aromatic pathway of E. coli. One of ordinary skill in the art would clearly not expect that the claimed method of increasing PEP availability by selecting cells which are phenotypically Pts-/glucose+ would increase the carbon flow into any metabolic pathway of the cell as many metabolic pathways within the cell do not utilize PEP as a precursor at all. Furthermore, even for those pathways for which PEP is a precursor, it is well known that the initial committed step of most metabolic pathways is highly regulated and usually rate limiting. As such, increasing the amount of upstream precursors of such pathways would not be expected to change the carbon flow into the pathway because the carbon flow into such pathways is controlled downstream. It is

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also noted that several of dependent claims include further modification of genes which encode enzymes which control other reactions which use or produce PEP in the cell (ppc, pyk, and pps). However, the possible effects of multiple mutations to increase the flux of PEP into a single metabolic pathway such as the common aromatic pathway are highly unpredictable as PEP is a necessary precursor for many other metabolic pathways and such multiple mutations may have unknown effects on these other pathways which would reduce cell growth. Furthermore, the specification describes only a single method of producing a phenotypically Pts cell comprising the modification or deletion of one or more of the host cell's PTS genes. However, one of ordinary skill in the art could not reasonably expect to make such mutations in any type of host cell as the PTS genes have been cloned from only a limited number of host cells. Applicants have not taught any method for selecting host cells mutated in these genes such that prior knowledge of the PTS genes would be unnecessary for selection of the Pts host cell. applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method for increasing the carbon flow from any carbon source into any metabolic pathway of any host cell. The scope of the claims must bear a reasonable correlation with

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the scope of enablement (<u>In re Fisher</u>, 166 USPQ 19 24 (CCPA 1970)).

Claims 1-22 are rejected under 35 U.S.C. \S 112, first paragraph, for the reasons set forth in the objection to the specification.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 17-19 are rejected under 35 U.S.C. \$ 102(b) as being anticipated by Biville et al. or Saier et al.

Biville et al. and Saier et al. each teach methods of selecting a $Pts^-/glucose^+$ cell comprising deleting the PTS genes (ptsH, ptsI, and crr), culturing the mutant cell using glucose as the sole available carbon source and selecting cells with a fast growth rate on glucose.

It should be noted that Claims 1 and 2 are included within the above rejection because the methods of Biville et al. and Saier et al. meet all process steps of applicants claimed processes, the method must inherently have the property of increasing carbon flow into a metabolic pathway by increasing PEP availability. The recitation "A method for increasing carbon flow into a metabolic pathway ... increasing PEP availability to the metabolic pathway" in Claim 1 has not been given patentable

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weight (with the exception of the phrase "of a host cell capable of utilizing a phosphotransferase transport system for carbohydrate transport" as this phrase provides a structural limitation on the type of host cell) because it has been held that a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim (i.e., the recited process steps in this case) does not depend on the preamble for completeness but, instead the process steps or structural limitations are able to stand alone. See MPEP 2111.02 citing In re Hirao 190 USPQ 15 (CCPA 1976), Kropa v. Robie, 88 USPQ 478 (CCPA 1951). In this case, the process steps, i.e., selecting a Pts / glucose + host cell (which host cell has the properties recited in the preamble) and culturing the selected host cell with an appropriate carbon source, clearly recite a complete process in and of themselves and thus are clearly able to stand alone. Doing these steps as Biville et al. and Saier et al. clearly did, inherently produces the effect recited in the preamble, i.e., increased PEP availability in the selected cell which produces increased carbon flow into biosynthetic pathways utilizing PEP as a precursor.

The following is a quotation of 35 U.S.C. \S 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that

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the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

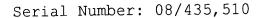
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. \S 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. \S 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. \S 102(f) or (g) prior art under 35 U.S.C. \S 103.

Claims 3, 5-16, and 20-22 are rejected under 35 U.S.C. \S 103 as being unpatentable over the combined disclosures of Frost, Holms and Biville et al. or Saier et al.

Frost teaches the amplification of carbon flow into the common aromatic pathway by increasing the amount of one of the substrates (E4P) for the first committed step of this pathway (i.e., the DAHP synthetase catalyzed condensation of E4P and PEP) by introduction of the transketolase gene into the host cell. He further teaches the introduction of one or more of the genes of the common aromatic pathway in such cells to further increase the amount of the desired final product.

Holms teaches that PEP within $E.\ coli$ is consumed by several different metabolic pathways (i.e., the PTS system, pyruvate

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synthesis by pyruvate kinase, and oxaloacetate synthesis by phosphoenolpyruvate carboxylase) and the amount of PEP channelled into each of these pathways. Holms teaches that the PTS system consumes 66% of the PEP produced while only 3% of the PEP pool is channelled into aromatic amino acid synthesis.

Biville et al. and Saier et al. teach methods of selecting a $Pts^-/glucose^+$ cell comprising deleting the PTS genes (ptsH, ptsI, and crr), culturing the mutant cell using glucose as the sole available carbon source and selecting cells with a fast growth rate on glucose.

The disclosure of Frost of amplification of carbon flow into the common aromatic pathway by increasing the amount of one of the substrates (E4P) for the first committed step of this pathway would suggest to the ordinary skilled artisan the amplification of the other necessary precursor (i.e., PEP) of this enzymatic step as one this would assure that neither substrate for this enzyme would be in limiting supply. One of ordinary skill in the art would recognize that the supply of any precursor used by a cellular pathway could be amplified by either increasing the amount of the precursor synthesized (such as done by Frost for E4P) or by preventing the depletion of the precursor by other cellular pathways thereby increasing the amount of the precursor available to be used by the desired pathway. The disclosure of Holms that 66% of the cellular PEP is used by the competing PTS pathway would suggest to the ordinary skilled artisan that PEP

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availability to the common aromatic pathway could be substantially increased by preventing PEP use by the PTS pathway. The disclosures of Biville et al. and Saier et al. each show that it is possible to produce cells which are deleted in the PTS system yet still retain high growth rates on glucose (a carbon source normally transported by the deleted PTS system). Therefore, it would have been obvious to one of ordinary skill in the art to produce a Pts / glucose mutant of the host cells of Frost which exhibit high levels of carbon flow into the common aromatic pathway as one of ordinary skill in the art would reasonably expect such a mutant cell to divert higher levels of the cellular pool of PEP into the aromatic amino acid biosynthetic pathways and produce further increases in the amount of carbon flow into this pathway. Furthermore, it would have been further obvious to one of ordinary skill in the art to further increase the amount of PEP diverted into this pathway by preventing its use by the other metabolic pathways which Holms teach that it is consumed by. As such it would have been obvious to further mutate the pyruvate kinase and pyruvate carboxylase genes as well.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca Prouty, Ph.D. whose telephone number is $(703)\ 308-4000$. The examiner can normally be reached on Monday-Friday from 8:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Wax, can be reached on (703) 308-4216. The fax phone number for this Group is (703) 305-7401.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

REDECCA E. PROUTY PATENT EXAMINER GROUP 1200

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